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Women with inherited mutations in BRCA1 or BRCA2 have significantly elevated risks of breast cancer. However, not all women with inherited BRCA1 or BRCA2 mutations develop breast or ovarian cancer, and among those who do, ages at cancer onset vary widely even within the same family. If a woman with a BRCA1 or BRCA2 mutation remains free of breast cancer for many years, it is possible that her status is due to chance, to modifying genes segregating in some families, or to environmental factors that influence risk. In this project, we evaluate environmental and lifestyle factors that could influence the impact of mutations in BRCA1 and BRCA2 on disease risk. It is possible that such co-factors identified among genetically predisposed women may be generalized to women who have not inherited predisposition to breast or ovarian cancer, because clinically and biologically, inherited cancer is virtually indistinguishable from its far more common, non-inherited counterpart.

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Mary Claire King 4.17.2000

PI - Signature Date

ENVIRONMENTAL AND LIFESTYLE INFLUENCES ON BREAST CANCER RISK: CLUES FROM WOMEN WITH INHERITED MUTATIONS IN BRCA1 AND BRCA2

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INTRODUCTION

Women with inherited disease-associated mutations in BRCA1 or BRCA2 have significantly elevated risks of breast cancer and of ovarian cancer. However, not all women with inherited BRCA1 or BRCA2 mutations develop breast or ovarian cancer, and among those who do, ages at cancer onset vary widely even within the same family. If a woman with a BRCA1 or BRCA2 predisposing mutation remains free of breast and ovarian cancer for many years, it is possible that her status is due to chance, to modifying genes segregating in some families, or to environmental factors that influence risk. In this project, we evaluate environmental and lifestyle factors that could influence penetrance of mutations in BRCA1 and BRCA2. It is possible that risk factors identified among genetically predisposed women may be generalized to women who have not inherited vulnerability to breast or ovarian cancer, because clinically and biologically, inherited cancer is virtually indistinguishable from its far more common, non-inherited counterpart.

BODY OF REPORT

Task 1. Send letters to eligible relatives explaining the study and inviting them to pre-test counseling.

Task 2. Provide pre-test counseling to relatives, administer informed consent and release forms for hospital records, obtain completed epidemiologic questionnaires, send blood samples to University of Washington for mutation analysis.

Task 3. Maintain database of contacts for participants and for those who decline after pre-test counseling.

By the end of the period covered by this report (Aug 31, 1999), 650 breast cancer patients entered the study as probands. Patients eligible to participate as probands are incident breast cancer patients of Jewish ancestry diagnosed at any of ten cancer centers in the greater New York area: Memorial Sloan Kettering Cancer Center, Beth Israel Medical Center, New York University Medical Center, Strang Cancer Prevention Center, Columbia Presbyterian Medical Center, Albert Einstein Medical Center, North Shore University Hospital, White Plains Hospital Center, Hackensack University Medical Center, or Stamford Hospital.

Each patient eligible to participate was offered pre-test genetic counseling and testing for inherited predisposition due to any of three ancient BRCA1 and BRCA2 mutations (BRCA1 185delAG, BRCA1 5382insC, BRCA2 6174delT). Each eligible patient who chose to participate provided information about her family history of breast cancer, completed the Environmental Factors Questionnaire, and provided a blood sample for DNA isolation. Our study coordinator, board-certified Genetic Counselor Jessica Mandell, M.S., supervised completion of Tasks 1, 2, and 3 at each of the collaborating sites.

For each proband identified with a BRCA1 or BRCA2 mutation, all adult relatives, regardless of cancer history, were offered the opportunity to participate in the project. Jessica Mandell provided pre-test genetic counseling for each of these relatives. Each relative who agreed to participate completed the Environmental Factors Questionnaire and

provided a blood sample. By the end date of the period covered by this report (Aug 31, 1999), 230 relatives from families with BRCA1 or BRCA2 mutations enrolled in the study.

Task 4. Genotype blood samples from participants for relevant mutations in BRCA1 and BRCA2.

In our laboratory at the University of Washington, BRCA1 and BRCA2 were genotyped for three founder mutations known to be common in the Jewish population. Frequencies of each mutation, by age of proband at diagnosis, are shown in Table 1.

Table 1. Proportion of probands with BRCA1 or BRCA2 mutations by age at diagnosis

	N	185delAG	5382insC	6174delT	any of 3
20-39	63	.11	.14	.08	.33
40-49	219	.07	.01	.05	.13
50-59	193	.03	.03	.02	.08
60-69	108	.00	.01	.00	.01
70+	67	.00	.00	.01	.01
Total	650	27	18	22	67
		.04	.03	.03	.10

The relationship between family history of breast cancer and presence of mutations in the probands is shown in Table 2.

Table 2. Proportion of probands with mutations by family history of cancer

	N	mutation	proportion
All probands	650	67	.10
Breast cancer			
mother	148	22	.14
sister <50	17	5	.29
male relative	14	4	.29
any 3 or more	41	8	.20
any relative	353		
Ovarian cancer			
mother	22	7	.32
sister	12	3	.25
any 2 or more	15	8	.53
any relative	64	17	.27
No relatives with breast or ovarian cancer	279	21	.08

Task 5. Report results of studies to patients as part of post-test genetic counseling.

Results of our genetic testing were reported to all probands in the context of post-test genetic counseling at their original cancer center. Results were reported to each participating relative in the context of post-test genetic counseling by Jessica Mandell, at a time and place convenient for the relative. Medical referrals for relatives with BRCA1 or BRCA2 mutations were arranged by Ms. Mandell through local cancer centers.

Task 6. Enter responses from questionnaire for use in analysis.

This task is in progress by Ming Lee, biostatistics coordinator for the project at the University of Washington, for all 650 probands and 230 relatives.

Task 7. Carry out statistical analyses of associations of epidemiologic risk factors and breast cancer incidence among mutation carriers and (for comparison) among relative not carrying mutations.

Evaluation of environmental exposures among genetically predisposed relatives is an analysis of gene-environment interaction, in that all individuals in the analysis carry a predisposing mutation. A powerful approach is to compare cumulative incidence of breast cancer by age among female mutation carriers with vs. without a specified risk factor. The project is enrolling participants at the rate expected, so by the end of the study, sample size will be adequate for these comparisons. In this reporting period, software was developed for the following analyses:

Lifetime risk of breast cancer, by mutation status
Lifetime risk of ovarian cancer, by mutation status
Association of age at menarche, age at first birth, and age at menopause with breast cancer incidence among women with mutations
Association of breastfeeding with breast cancer incidence among women with mutations
Association of oral contraceptive use with breast cancer incidence among women with mutations
Association of hormone replacement therapy with breast cancer incidence among women with mutations
Association of exposure to cigarette smoke (either smoking history or indirect exposure) with breast cancer incidence among women with mutations
Association of alcohol consumption with breast cancer incidence among women with mutations
Association of alcohol consumption with breast cancer incidence among women with mutations
Association of occupational exposure to radiation with breast cancer incidence among women with mutations
Association of occupational or household exposure to pesticides with breast cancer incidence among women with mutations

KEY RESEARCH ACCOMPLISHMENTS

650 incident breast cancer patients of Jewish ancestry have been enrolled in our study, received genetic counseling, completed the Environmental Factors questionnaire, and been genotyped for the three ancient Jewish BRCA1 and BRCA2 mutations.

Genotypes have been reported back to all participants requesting this information in the context of post-test counseling.

Among our probands, 67 carry one of the three ancient BRCA mutations. Mutations are more frequent among probands with younger ages at diagnosis.

230 relatives from these 67 families with BRCA1 or BRCA2 mutations have been enrolled and genotyped.

Environmental Factors Questionnaires of probands and their relatives have been collected and are being encoded for statistical analysis. Software for statistical analyses has been developed.

REPORTABLE OUTCOMES

No publications from study as of August 31, 1999

Jessica Mandell, M.S., received her board certification as a genetic counselor from the American Board of Genetic Counseling and Medical Genetics.

CONCLUSIONS

Evaluation of environmental effects which might influence risk of breast cancer are ongoing.